6 Pregnancy Morbidity Associated with Hereditary and Acquired Thrombophilias: Late Obstetric Complications

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Abstract

As well as being associated with recurrent miscarriage (RM), antiphospholipid antibodies (aPL) are associated with late placental vascular-mediated pregnancy complications such as severe pre-eclampsia, intrauterine growth restriction (IUGR), abruptio placentae, late fetal loss, and stillbirth. There are also associations between heritable thrombophilias and these late pregnancy complications. Finally, venous thromboembolism (VTE) in pregnancy, as in the non-pregnant state, is linked to thrombophilia. In this review, potential adverse effects of thrombophilia in late pregnancy are discussed. Preliminary data suggest that maternal antithrombotic prophylaxis may result in improved pregnancy outcome in selected cases. Randomized trials are needed to evaluate treatment strategies.

6.1 Introduction

Thrombophilic risk factors are common and can be found in approximately 20 % of Caucasian populations. Since pregnancy is an acquired hypercoagulable state, women harboring thrombophilia may present with clinical symptoms of vascular complications for the first time during gestation or the postpartum period. This chapter will focus on different types of thrombophilia and their association with placental vascular complications including preeclampsia, IUGR, placental abruption, and late fetal loss (fetal loss above 24 weeks' gestation is defined as stillbirth and fetal loss between 20 and 24 weeks is generally described as late fetal loss). The reader should also refer to Chap. 2. on heritable and acquired thrombophilias.

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6.2 Hemostatic Changes in Normal Pregnancy

For a detailed description, the reader should refer to Chap. 1. There is a marked increase in blood pro coagulant activity, characterized by an elevation of factors VII, X, VIII; fibrinogen; and von Willebrand factor [14], especially at

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Table 6.1 Classification and prevalence of thrombophilia

	Thrombophilia	% of general population
Inherited	Antithrombin deficiency	0.07
	Protein C deficiency	0.3
	Protein S deficiency	0.2
	Factor V Leiden (heterozygous)	4
	Factor V Leiden (homozygous)	0.06
	Prothrombin gene mutation	2
Acquired	Antiphospholipid antibodies (Lupus anticoagulant Anticardiolipin antibodies)	2
	Acquired APC resistance without factor V Leiden	3.3

term in normal pregnancy. This is associated with an increase in prothrombin fragment F1.2 and thrombin-antithrombin complexes [15, 87]. There is a decrease in physiologic anticoagulants manifested by a significant reduction in protein S activity and [21] by acquired activated protein C resistance (APCR) [23]. The overall fibrinolytic activity is impaired during pregnancy but rapidly returns to normal following delivery [110]. This is largely due to placenta-derived plasminogen activator inhibitor type 2 (PAI-2), which is present in substantial quantities during pregnancy [55]. D-dimer, a specific marker of fibrinolysis resulting from breakdown of cross-linked fibrin polymer by plasmin, increases as pregnancy progresses [35]. Overall, there is a five- to ten-fold increased risk of VTE throughout gestation and the postpartum period.

Thrombophilias can be either inherited or acquired. The prevalence of these thrombophilias in the general population is depicted in Table 6.1.

6.3 Heritable Thrombophilia

Table 6.1 lists the congenital thrombophilic factors most frequently associated with obstetric complications. For details on heritable thrombophilias, the reader should refer to Chap. 2. The prevalence of the factor V Leiden (FVL) mutation is very low in Asian and African populations, and around 4% higher in Caucasians. However, APCR may be present in pregnancy without FVL; the reported prevalence ranges from 50 % [107] to 95 % [8]. The frequency of the prothrombin gene mutation increases geographically from Northern to Southern Europe [119]. The prevalence of heterozygosity for the G20210A prothrombin gene mutation is 2 % [117]. Protein S and protein C deficiencies are quite rare, and carriers have a significantly increased risk of thrombosis when the inhibitory effect on coagulation is lost [22, 67]. Antithrombin (AT) deficiency may be the result of many different mutations and has a prevalence of 0.07 %. It is the most thrombogenic of the inherited thrombophilias, with a reported 70–90 % lifetime risk of thromboembolism in individuals with type 1 AT deficiency [22, 67]. Homozygosity for the C677T methylenetetrahydrofolate reductase (MTHFR) polymorphism has an observed prevalence varying from 15.2 % in Hispanic populations to 10.2 % in Caucasians, 8.8 % in Asians, and 2.4 % in African Americans [117]. Several alleles (C and T) have been described. Homozygosity for the T variant results in elevated homocysteine levels, which can cause vascular injury [117]. The plasminogen activator inhibitor (PAI) 4G/4G polymorphism has a reported prevalence of around 25 % [35]. PAI 4G/4G inhibits the activation of plasminogen to the fibrinolytic enzyme plasmin. The resulting decreased fibrinolytic activity would potentially increase the risk of thrombosis [35], but the clinical significance of this polymorphism remains uncertain.

6.4 Acquired Thrombophilia

6.4.1 The Antiphospholipid Syndrome and Late Pregnancy Complications

The international consensus statement on revised criteria (Sapporo) for the diagnosis of obstetric antiphospholipid syndrome (APS) is based on clinical criteria for the diagnosis of APS with laboratory findings of persistent medium- or high-titer antiphospholipid antibodies (aPL) that are present on two or more occasions at least 12 weeks apart [75]. Women with aPL may present with

Table 6.2 Revised Sapporo criteria (international consensus statement) for the diagnosis of antiphospholipid syndrome [75]

Clinical criteria (one or more)
1. *Vascular thrombosis*: One or more objectively confirmed episodes of arterial, venous or small vessel thrombosis occurring in any tissue or organ
2. *Pregnancy morbidity*: (a) One or more unexplained deaths of a morphologically normal fetus ≥10th week of gestation; or (b) One or more premature births of a morphologically normal neonate <34th week of gestation because of eclampsia, pre-eclampsia or placental insufficiency; or (c) Three or more unexplained consecutive miscarriages <10th week of gestation
Laboratory criteria (one or more, present on two or more occasions at least 12 weeks apart using recommended procedures)
1. Lupus anticoagulant (LA), detected according to the guidelines of the International Society on Thrombosis and Haemostasis
2. Anticardiolipin antibody (aCL) of IgG and/or IgM isotype, present in medium or high titre (>40 GPL or MPL, or >99th percentile), measured by a standardized ELISA
3. Anti-β2-glycoprotein-1 antibody (anti-β2-GP1) of IgG and/or IgM isotype, present in titre >99th percentile, measured by a standardized ELISA

either recurrent miscarriage (RM) [86, 95] (in up to 20 %) [11, 86, 96] or fetal demise beyond 10 weeks of gestation [84], and aPL are also associated with one or more of the following: eclampsia, pre-eclampsia or IUGR, with the criteria for late obstetric morbidity in APS in Table 6.2. In a study of 60 pregnancies in women with APS, the most specific clinical features were reported to be thrombosis (both venous and arterial), RM, fetal loss in the second and third trimesters, and autoimmune thrombocytopenia [64].

Pregnancy morbidity in the form of fetal loss or premature birth is a relatively common finding in women with APS [85]. The mechanism of fetal loss is believed to be due to binding of antiphospholipid antibodies to trophoblast cells, resulting in defective placentation [27]. Thrombotic complications within the uteroplacental circulation have also been proposed as a contributing mechanism [42, 96]. APS is associated with placental vascular thrombosis, decidual vasculopathy, intervillous fibrin deposition, and placental infarction [49, 96]. These pathological changes in the placenta may result in RM, early severe pre-eclampsia, IUGR, or stillbirth. A positive test result for anticardiolipin antibodies (aCL) or presence of lupus anticoagulant (LA) may be found in 10–15 % of women with fetal death beyond 20 weeks of gestation [9, 13, 84].

The relation between APS and pre-eclampsia has been shown in several studies [13, 26, 108]. aCL were detected in 21 % of more than 300 patients with severe pre-eclampsia [112], with a 27.4 % incidence in the group who delivered before 28 weeks' gestation and a 19.3 % incidence in the group who delivered after 28 weeks. As low positive IgG and/or IgM titers were noted in 20 % of controls, the authors concluded that 16 % is a realistic estimate of the incidence of aCL-positivity in patients with a history of severe pre-eclampsia, which is concordant with the findings of other studies [10, 56, 89]. Most studies found an association with positive tests for aCL and early-onset severe pre-eclampsia, and testing in these patients may have therapeutic implications for future pregnancies. Conversely, other investigators did not find a correlation between APS and pre-eclampsia [68, 85]. Women with APS are also at substantial risk (increased by approximately 30 %) of IUGR [10, 90]. In one study, 24 % of mothers who delivered an IUGR infant had medium or high positive test results for aCL [90].

6.5 Placental Findings Associated with Thrombophilias and Pregnancy Complications

A research group from Tel Aviv [70] described placental findings in women who had severe complications during pregnancy and were carriers of thrombophilias, and compared them to women with severe complications during pregnancy without thrombophilia. The study population consisted of 68 women with singleton pregnancies who had severe pre-eclampsia, IUGR, abruptio placentae, or stillbirth. They were evaluated after delivery for the presence of mutations of FVL, C677T MTHFR, prothrombin G20210A, and deficiencies of protein S, protein C, and AT. All were negative for aPL. Thirty-two women carried a thrombophilia and 36 women did not. All placentas were

evaluated by a single pathologist who was blinded to the results of the thrombophilia assessment. There was no difference in the maternal age, parity, type of pregnancy complication, and fetoplacental weight ratio between the groups. The proportion of women with villous infarcts was significantly higher in women with thrombophilias (72 % vs. 39 %, $p<0.01$), as was the proportion of women with multiple infarcts or fibrinoid necrosis of decidual vessels. Conversely, in a recent study with a very similar design which also examined the relationship between placental histology and thrombophilia in women with severe complications, no specific histological pattern could be identified when thrombophilia-positive and thrombophilia-negative groups were compared [77]. Nevertheless, a high rate of placental infarcts (50 %) and thrombosis was confirmed in women both with and without thrombophilias. Likewise, placental pathology in early-onset pre-eclampsia and IUGR was similar in women with and without thrombophilia although a high rate of placental abnormalities was found [109, 118]. Arias et al. (1999) evaluated 13 women with thrombotic lesions of the placenta [4]. All women had obstetric complications such as pre-eclampsia, preterm labor, IUGR, or stillbirth. In 10 of the 13 (77 %), an inherited thrombophilia was found; 7 were heterozygous for the FV Leiden mutation and 3 had protein S deficiency. The most prominent placental lesions were fetal stem vessel thrombosis, infarcts, hypoplasia, spiral artery thrombosis, and perivillous fibrin deposition [4].

6.6 Thrombophilia and IUGR

IUGR is an important cause of perinatal morbidity and mortality. Growth-restricted infants are at increased risk of developing neuropsychological defects and suffering educational disadvantages later in childhood [46, 98]. Moreover, there is epidemiological evidence that children whose intrauterine growth was restricted have a higher risk of cardiovascular and endocrine diseases in adulthood [5]. An association between obstetric complications and heritable causes of thrombophilia has been reported [40, 114] (Table 6.3). Kupferminc et al. (1999) reported an association between inherited thrombophilia (FVL, prothrombin G20210A, MTHFR) and IUGR (defined as a birth weight below the 5th percentile for gestational age) [56]; an association was demonstrated in women with severe IUGR but not in milder cases. Martinelli et al. (2001) compared 63 women with a history of IUGR, defined as birth weight below the 10th percentile, and 93 parous women with uneventful pregnancies. Among women with IUGR, 13 % had FVL compared with 2.2 % of controls (OR, 6.9; 95 % CI 1.4–33.5), and 12 % had the

Table 6.3 Association of thrombophilia with placental vascular complications

	IUFD	Severe IUGR	Severe pre-eclampsia	Abruption
Antithrombin deficiency	I+ (98, 105)	II+	II+	III+
Protein C deficiency	II+ (98, 106)	ND	ND	II+ 4
Protein S deficiency	I+ (98, 105, 106)	II+ (28)	II+ (28)	III+ (25)
APC resistance	I+ (116)	II+	II+	II+ (116)
Factor V Leiden	I+ (107, 116)	II+ (40, 114)	I+ (28, 30, 54, 65, 78)	II (53, 116)
MTHFR 677TT	I– (28)	II– (28, 113)	II– (27, 28, 41, 82, 113)	II–
Hyperhomocysteinemia	I+ (28, 113)	II+ (28, 113)	II+	II+ (25, 113)
Factor II 20210G_A	I+ (77, 107)	II+ (43, 54, 59)	II+ (47, 76)	II+ (59, 99)
Antiphospholipid antibodies	I+ (45)	II+ (58)	II+ (9, 27, 58)	II+ (58)
Combined defects	I+ (47, 69, 98)	II+ (58)	II+ (58)	II+ (58)

Reference numbers are listed in parentheses

Level I (*I*) indicates that the recommendation is based on one or more well-designed prospective studies or two or more well-designed retrospective studies; level II (*II*), the recommendation is based on retrospective studies that reach consensus; level III (*III*), the recommendation is based on isolated anecdotal studies and/or the consensus of expert practitioners

+ association present, – association not present, *ND* no data, *MTHFR* methylenetetrahydrofolate reductase

G20210A prothrombin mutation compared with 2.2 % of controls (OR, 5.9; 95 % CI 1.2–29.4). In a regression-analysis model, these thrombophilias were independently associated with IUGR [72]. A later report from the same group [40] tested for these mutations in neonates weighing less than 2.5 kg. Neonates delivered by mothers with FVL or prothrombin mutations accounted for 30 % of newborns weighing less than 1 kg, 18.7 % of those ranging from 1.001 to 2.499 kg, and only 9.5 % of those weighing 2.5 kg or more. Overall, 27.6 % of neonates of mothers with the mutations weighed less than 2.5 kg compared with 13.9 % of neonates of mothers without mutations (OR, 2.4; 95 % CI 1.5–3.7). However, other studies failed to confirm an association between IUGR and thrombophilic mutations [50]. In one such study [50], the prevalence of thrombophilia in mothers of 493 newborns with IUGR (<10th percentile) and 472 controls did not differ significantly. However, one third of the study population was not Caucasian and the degree of IUGR was mild, with mean birth weight of 2.393 ± 0.606 kg and 83 % of newborns delivered at 36–40 weeks' gestation. In contrast, in the study by Kupferminc et al. (1999), the mean birth weight was 1.387 ± 0.616 kg and mean gestational week at delivery was 33 ± 4.0 [56]. Similarly, Martinelli et al. (2001) reported a mean gestational week at delivery of 35 ± 3 and a mean birth weight of 1.584 ± 0.586 kg [72]. It is therefore suggested that these studies are dealing with noncomparable fetal and neonatal populations with different clinical relevance. Several meta-analyses suggest a strong association between thrombophilia and IUGR [1, 30, 48, 53, 102]. On the other hand, a large cohort study and prospective studies found no significant association [19, 29, 66, 73].

6.7 Thrombophilia and Pre-eclampsia

The association of pre-eclampsia with thrombophilia is similarly controversial; a number of case–control studies demonstrate an association, while others fail to do so. Women with FVL and severe pre-eclampsia may have a higher risk of serious maternal complications and adverse perinatal outcomes than those without thrombophilia [28, 32, 38, 74, 105] (Table 6.3). An association between the presence of FVL and a history of severe forms of pre-eclampsia has been reported [30]. One study demonstrated an increased prevalence of thrombophilia (65 %) in women with severe pre-eclampsia compared with controls (18 %) [56]. There was a higher prevalence of thrombophilic polymorphisms including FVL, prothrombin G20210A, and MTFHR in women presenting with pre-eclampsia [47, 52, 56]. The same study also highlighted that women with other obstetric complications had a significantly higher incidence of combined thrombophilias. In a sample of 140 Italian women with a history of gestational hypertension, with or without significant proteinuria, a significantly higher prevalence of thrombophilias was documented regardless of the presence of proteinuria [39]. Logistic regression showed that FVL and prothrombin G20210A mutations were independently associated with occurrence of gestational hypertension.

A recent meta-analysis has confirmed an association between FVL or prothrombin G20210A and severe early-onset pre-eclampsia [76]. Several studies have reported an association between HELLP syndrome and thrombophilia (and the FVL mutation in particular), with a frequency (compared with controls) of 7.9 % vs. 1.8 % [78], 7.2 % vs. 4.5 % [41], and 20 % vs. 6 % ($p = 0.003$) [7, 78, 83]. In larger meta-analyses, heterozygosity for the FVL mutation was associated with a twofold increased risk [30, 54, 65, 102]. However, these risk estimates were based on pooled data from contradictory studies. These conflicting results may be due at least in part to differences in the severity of pre-eclampsia [74, 76]. A more recent meta-analysis of six cohort studies found a modest but statistically significant increase in the risk of pre-eclampsia in women with a FVL mutation (OR = 1.49) [29]. Many studies suggest that FVL has a stronger association with severe and early-onset pre-eclampsia than with milder forms of the disease [50, 72, 78]. Furthermore, a recent prospective cohort study suggests that FVL was associated with a six- to seven-fold increased risk of recurrent

severe pre-eclampsia, which occurred in 59 % of heterozygous women [32].

In contrast, several studies found no association between FVL and pre-eclampsia [2, 76]. FVL did not increase the risk of pre-eclampsia in six prospective studies of unselected women screened during pregnancy [19, 29, 52, 66, 79]. Histopathologic features of placental insufficiency were found in 63 % of women with pre-eclampsia but were not associated with the FVL mutation [52].

The G20210A prothrombin gene mutation has been variously reported in 11.4 % of women with pre-eclampsia vs. 4.1 % of controls (OR = 2.96) [51], 10 % vs. 3 % ($p = 0.03$) [7], and 13 % vs. 3.2 % ($p = 0.001$) [59]. This mutation was more prevalent in women with IUGR ($p = 0.0009$), placental abruption ($p = 0.01$), and second-trimester loss ($p = 0.001$), but not in women with severe pre-eclampsia, third-trimester loss, and recurrent early fetal loss [59].

Women with FVL appear to be at a small absolute increased risk of late pregnancy loss. Women with FVL and PGM appear not to be at increased risk of pre-eclampsia or birth of a small for gestational age (SGA) infant [103].

Homozygosity for the MTHFR polymorphism was found in 22 % of cases of pre-eclampsia compared with 8 % of controls ($p = 0.005$) [7]. The frequency of any inherited thrombophilia in pre-eclamptic women has been estimated to be as high as 56 % [59] and 52 % [7] vs. 19 % in controls, and as high as 69 % in women with severe IUGR in the second trimester vs. 4 % in controls ($p = 0.001$) [58]. Other studies failed to find an association between a common genetic risk factor for thrombosis and the occurrence of pre-eclampsia [24]. However, these studies seem to differ in selection of controls and in ethnic backgrounds. The size of these studies of pre-eclampsia is generally small, especially if the aim was to detect any possible association between the less frequent thrombophilias, such as protein S, protein C, and AT deficiencies, and obstetric complications. Those studies reporting a significant association are generally smaller (31–140 study subjects) than those reporting a lack of association (15–707 subjects). In many of the studies, groups of different thrombophilias or complications are pooled together, which sometimes results in significant associations that do not remain significant when the relevant subgroups are analyzed separately. The pooling of study subjects can lead to inaccuracy in determining the exact impact of a specific mutation on each of the complications.

Nonetheless, overall these data suggest that, while prothrombotic genotypes might not be causative factors for pre-eclampsia, they could be linked to the severity of disease expression once the condition arises.

6.8 Thrombophilia and Placental Abruption

Van der Molen et al. (2000) investigated coagulation inhibitors and abnormalities of homocysteine metabolism as risk factors for placental vasculopathy [111]. They compared non-pregnant women with a history of placental vasculopathy with non-pregnant controls. Protein C activity was noted to be significantly lower in women that had adverse pregnancy outcome. Homozygotes for the MTHFR polymorphism and carriers of the FVL mutation were significantly more common in the study group. The median levels of homocysteine, APCR ratio, protein S, and AT were not different between the groups. However, homocysteine levels above 14.4 μmol/L (the 80th percentile of control values) were associated with a significant increase in OR. Also, combination of risk factors such as homocysteine levels above 14.4 μmol and protein S deficiency resulted in a significantly increased OR for placental vasculopathy. The risk factors for placental vasculopathy which emerge in this study are APCR and decreased levels of protein C, elevated homocysteine, and the C677T MTHFR polymorphism, or a combination of these.

Wiener-Megnagi et al. (1998) studied 27 women who had placental abruption and 29 controls and found that 63 % of cases had an APCR ratio ≤ 2.5 compared with 17 % of controls (OR 8.16, $p = 0.001$) [116]. Eight of 15 patients

(53 %) tested were found to have the FVL mutation (5 heterozygous and 3 homozygous) compared with 1 heterozygote among the control subjects (3.4 %). Similarly, Kupferminc et al. (1999) found a 70 % incidence of thrombophilias in women with placental abruption [56], of which 60 % had thrombophilic mutations and 10 % had AT deficiency or APS. Of the 20 women who had an abruption, 3 also had mild pre-eclampsia, 7 had antepartum or postpartum hypertension, and 11 of the neonates were below the 10th percentile for gestational age. In this study, which was the first to examine the G20210A prothrombin gene mutation in women with pregnancy complications, the OR for abruption with this mutation was 8.9 (95 % CI 1.8–43.6), whereas the ORs for the FVL mutation and MTHFR polymorphism were 4.9 (95 % CI 1.0–17.4) and 2 (95 % CI 0.5–8.1), respectively. In another study, the incidence of the prothrombin gene mutation in 27 women with placental abruption was 18.5 % compared to 3.2 % of controls (OR, 5.8; 95 % CI 1.8–18.6, $p=0.01$) [59]. In the study by de Vries et al. (1997), 26 % of women with placental abruption had hyperhomocysteinemia and 29 % protein S deficiency [25, 36, 113].

Prochazka et al. (2003) reported that FVL carrier status was not significantly different in women with placental abruption but was associated with a positive family history of venous thrombosis [92]. However, the same group reported that 20 of 142 (14.1 %) women with placental abruption were heterozygous for FVL, compared to 10 of 196 (5.1 %) of controls (OR 3.0, 95 % CI 1.4–6.7) [93]. Association with FVL may be stronger for placental abruption that occurs at earlier gestations [53]. In a meta-analysis, heterozygosity for FVL was associated with a nearly fivefold increased risk of placental abruption [33, 102]. Several other studies found no significant association [3, 66, 81].

Analysis of The New Jersey-Placental Abruption Study (2002–2007) suggests that women with lower protein C levels (<5th centile) had an increased risk of abruption, with an OR of 3.2 (95 % CI 1.2–9.9) [4]. Reduction in both protein S and APCR ratio was not associated with abruption (Table 6.3).

6.9 Thrombophilia and Late Fetal Loss

Preston et al. (1996) reported increased fetal loss in women with heritable thrombophilic defects [88, 91, 100] (Table 6.3). The authors studied 1,384 women enrolled in the European Prospective Cohort on Thrombophilia (EPCOT). Of 843 women with thrombophilia, 571 had 1,524 pregnancies; of 541 control women, 395 had 1,019 pregnancies. The authors analyzed the frequency of fetal loss (<28 weeks of gestation) and stillbirth (>28 weeks of gestation) jointly and separately. The risk of fetal loss was increased in women with thrombophilia (OR, 1.35, 95 % CI 1.01–1.82). The OR was higher for stillbirth than for miscarriage (3.6; 95 % CI 1.4–9.4 vs. 1.27; 95 % CI 0.94–1.71). The highest OR for stillbirth was in women with combined defects (OR, 14.3; 95 % CI 2.4–86.0) compared with 5.2 (1.5–18.1) in AT deficiency, 2.3 (0.6–8.3) in protein C deficiency, 3.3 (1.0–11.3) in protein S deficiency, and 2.0 (0.5–7.7) with FVL. The authors concluded that women with familial thrombophilia, especially those with combined defects or AT deficiency, have an increased risk of fetal loss, particularly stillbirth.

Gris et al. (1999) performed a case–control study in 232 women with a history of one or more second- or third-trimester losses and no history of thrombosis who were matched with 464 controls and tested for thrombophilias and APS [45]. They found at least one thrombophilia in 21.1 % of the patients and in 3.9 % of the controls ($p<0.0001$), with an OR of 5.5 (95 % CI 3.4–9.0) for stillbirth in women positive for any thrombophilia. After logistic regression analysis, four adjusted risk factors for stillbirth remained: protein S deficiency, anti-beta2 glycoprotein IgG antibodies, aCL IgG antibodies, and the FVL mutation.

Multiple other studies and four meta-analyses suggest that FVL heterozygotes have a higher relative risk of late pregnancy loss than early first-trimester loss [30, 53, 99, 103, 107]. A meta-analysis found that heterozygosity for FVL is associated with a twofold increased risk of late unexplained fetal loss and a fourfold higher risk of loss in the second trimester compared to the first trimester [102]. One possible explanation is that late

pregnancy losses reflect thrombosis of the placental vessels, in contrast to first-trimester losses, which are more commonly attributable to other causes, in particular fetal chromosome abnormality. In several studies, the majority of placentas from women heterozygous for FVL and with a late fetal loss had evidence of thrombotic vasculopathy or infarction, supporting this hypothesis [45, 71].

In a study of 18 pregnancies with AT deficiency [105, 106], 10 suffered an adverse outcome (55.6 %), including stillbirth (11.1 %), IUGR (33.3 %), abruption (6.7 %), and pre-eclampsia (6.7 %). A lower incidence of pregnancy complications was observed among women with antithrombotic treatment [105].

Kupferminc et al. (1999) found a 50 % prevalence of thrombophilias in women with intrauterine fetal death (IUFD) occurring after 23 weeks' gestation [56]. A recent study tested 67 women with fetal loss after 20 weeks of pregnancy and 232 controls, for FVL, prothrombin gene mutation, and MTHFR mutation. Sixteen percent of the 67 women with fetal loss and 6 % of the controls had either the FVL or the prothrombin gene mutation. The relative risks of late fetal loss in carriers of the FVL and prothrombin gene mutations were 3.2 (95 % CI 1.0–10.9) and 3.3 (95 % CI 1.1–10.3), respectively. Placental investigation showed histological evidence of thrombosis in 76 % of placentas examined [71]. A study that investigated women with IUFD at 27 weeks' gestation or more found that, in 40 women with unexplained IUFD, the prevalence of inherited thrombophilias was 42.5 % compared with 15 % in controls (OR, 2.8; 95 % CI 1.5–5.3, $p = 0.001$) [69].

6.10 Management of Adverse Pregnancy Outcome Associated with Thrombophilia

The management of the obstetric patient with thrombophilia is complex [20, 104, 115] (Table 6.4). Many women with an underlying thrombophilia are healthy, while many others without any known thrombophilia experience medical and obstetric complications. The risk of thromboembolism and adverse pregnancy outcomes seems to arise from an interplay of medical, obstetric, and family history, along with genetic and environmental factors. Futhermore, current treatment with low molecular weight heparin (LMWH) when used as prophylactic or therapeutic anticoagulation , is not without risks such as the potential for bleeding and allergies, and is inconvenient.

Table 6.4 Observational studies on prevention of poor gestational outcome in carriers of thrombophilia

Patients, *n*	Thrombophilia	Obstetric history	Treatment	Live birth with normal outcome	Reference no.
60	APS	RFL	LMWH LDA	70 %	Lima et al. [64]
50	Inherited and acquired	RFL	Enoxaparin (LDA for APS)	46/61 (75 %)	Brenner et al. [17]
25	Factor V Leiden or factor II 20210GA	RFL pre-eclampsia IUGR	UFH or LMWH or LDA	29/31 (93 %)	Grandone et al. [37]
33	Not specified	Pregnancy complications	40 mg enoxaparin LDA	30/33 (91 %)	Kupferminc et al. [57]
26 Patients vs. birth weight	Inherited and acquired	Pregnancy complications	40 mg enoxaparin LDA	Higher birthweight with LMWH	Riyazi et al. [101]
160	Inherited and acquired	Pregnancy complications	40 mg enoxaparin LDA	Higher birth weight with LMWH	Gris et al. [44]
160	Inherited	Abruption	40 mg enoxaparin	Lower incidence of pregnancy complications	Gris et al. [43]

APS antiphospholipid syndrome, *LDA* low-dose aspirin, *RFL* recurrent fetal loss, *IUGR* intrauterine growth restriction

Screening for acquired thrombophilia (APS) is recommended in women who suffer recurrent first-trimester miscarriage or who have had late fetal losses, particularly if associated with features of placental thrombosis or infarction, and those who suffer one or more premature births of a morphologically normal neonate <34th week of gestation because of eclampsia, pre-eclampsia, or IUGR [75]. This is because evidence is accumulating for a beneficial effect of aspirin and heparin to prevent RM [60, 94] and fetal loss [13, 61, 64] in APS. Prospective studies of women with previous poor pregnancy outcome, including late fetal death and neonatal death, demonstrate that the use of aspirin and/or heparin combined with judicious monitoring and timely intervention results in an improved live birth rate from 12 to 69 % [13] and from19 to 70 % [64].

A Cochrane review [51] revealed a paucity of studies on the efficacy and safety of aspirin and heparin in women with a history of RM without apparent causes other than inherited thrombophilia. Therefore, the use of anticoagulants in unexplained RM is not recommended. Conversely, in heritable thrombophilia, our knowledge of the optimal treatment (except for the role of low-dose aspirin: see below) during pregnancy is limited. The data suggest that certain risk groups should be screened for thrombophilia, as the evidence suggests that there is a high recurrence rate of complications in future pregnancies in women who previously experienced adverse pregnancy outcome and carry a thrombophilia [37]. These at-risk groups include women with a personal or family history of thromboembolism, recurrent first- and second-trimester loss, severe pre-eclampsia, IUGR, stillbirth, or abruptio placentae. Ideally, testing should take place between pregnancies since protein S levels fall and APCR increases during normal pregnancy [18].

The Cochrane Collaboration (2001) demonstrated that the use of low-dose aspirin is associated with a 17 % reduction in the risk of pre-eclampsia (32 trials with 29,331 women, relative risk [RR] 0.85; 95 % CI 0.78–0.92) and a 14 % reduction in the risk of fetal or neonatal death (30 trials with 30,093 women, RR, 0.86; 95 % CI 0.75–0.99). This reduction in fetal and neonatal death was greatest among high-risk women (4,134 women, RR, 0.73; 95 % CI 0.56–0.96) [31]. However, the combined role of low-dose aspirin and heparin treatment in inherited thrombophilia, particularly in later pregnancy, has not been evaluated in randomized controlled trials. Many studies suggest that they may have a complementary role.

In a large retrospective cohort study performed by North et al. (1995), women with renal disease in pregnancy were allocated to a "no-treatment" control group, a low-dose aspirin group, or a group that received prophylactic heparin combined with aspirin and/or dipyridamole [82]. Pre-eclampsia was less common in the heparin group compared with the no-treatment group and the aspirin group.

Another study by Kupferminc et al. (2001) included women with known thrombophilia and a history of severe pre-eclampsia, abruption, IUGR, or stillbirth [57]. Women were treated with enoxaparin 40 mg/day and aspirin 100 mg/day from 8 to 12 weeks' gestation onward. The mean gestational age at delivery in the untreated women was 32.1 ± 5.0 weeks as compared to 37.6 ± 2.3 weeks in women treated with enoxaparin ($p < 0.001$). The mean birth weight of the infants from the control group was 1.175 ± 0.59 kg compared to 2.719 ± 0.526 kg in the treated women ($p < 0.001$). Pregnancy complications occurred in only 9 % of women, and neither severe pre-eclampsia nor perinatal deaths occurred in the treated women [57].

Similarly, favorable effects were suggested in a small study that evaluated treatment with LMWH combined with aspirin in pregnant women with thrombophilia and a history of early-onset pre-eclampsia and/or IUGR [101]. Pregnant women with thrombophilia were randomized to low-dose aspirin and LMWH ($n = 26$) or aspirin alone ($n = 19$). There was no difference in the overall birth weight between the groups. However, when considering the 18 patients with a single thrombophilia (i.e. excluding 8 patients with multiple thrombophilias), birth weights were significantly higher ($p = 0.019$) compared to the 19 with no coagulation abnormality. In addition, two perinatal deaths occurred in the aspirin group vs. no perinatal death in the aspirin plus LMWH group. These preliminary studies suggest that LMWH may have an additional beneficial effect on the pregnancy

outcome of women with a history of severe pre-eclampsia and/or IUGR and documented thrombophilia.

In the Live-Enox study, the incidence of pre-eclampsia, placental abruption, and IUGR was substantially lower with LMWH prophylaxis than in prior untreated pregnancies [16, 17]. A favorable effect on birth weight was noted in women with thrombophilia and prior fetal loss that were treated with LMWH and aspirin [44]. A randomized trial studied the effect of LMWH prophylaxis in women with thrombophilia and previous adverse pregnancy outcome. LMWH significantly reduced the incidence of the severe pre-eclampsia, IUGR, abruption, and IUFD after 20 weeks [99].

A pilot study investigated the effectiveness of enoxaparin in women with a previous placental abruption and inherited thrombophilia. Women were randomized to either a prophylactic daily dose of enoxaparin starting from the time of a positive pregnancy test ($n=80$) or no enoxaparin ($n=80$). Enoxaparin was safe, with no obvious side-effects such as thrombocytopenia or major bleeding events. Furthermore, enoxaparin reduced the occurrence of placental vascular complications [43].

Leeda et al. (1998) studied the effects of folic acid and vitamin B6 supplementation in women with hyperhomocysteinemia and a history of pre-eclampsia or IUGR [63]. A total of 207 consecutive patients with a history of pre-eclampsia or IUGR were tested for hyperhomocysteinemia. Thirty-seven were found to have raised levels and were treated with folic acid and vitamin B6, and 27 had a second methionine-loading test after vitamin supplementation. This showed that 14 patients became pregnant while receiving vitamin B6, folic acid, and aspirin; 7 of these 14 were complicated by pre-eclampsia. Birth weights were 2.867 ± 0.648 kg compared with 1.088 ± 0.57 kg in the previous pregnancies ($p<0.001$). Therefore, in women with hyperhomocysteinemia and a history of pre-eclampsia or IUGR, vitamin B6 and folic acid can correct the methionine-loading test and appear to have a favorable effect on birth weight, but not pre-eclampsia.

Presence of moderate quality evidence, the American College of Chest Physicians (ACCP) guidelines recommend low-dose aspirin throughout pregnancy for women at risk of pre-eclampsia. Unfractionated or LMWH are not recommended for thrombophilic women with a history of pre-eclampsia or other adverse pregnancy outcomes [6].

The findings of the FRUIT trial, (FRactionated heparin in pregnant women with a history of Utero-placental Insufficiency and Thrombophilia), a randomized controlled trial, have been published. This study found that adding LMWH to aspirin before 12 weeks of gestation reduces the risk of recurrence of pre-eclampsia with onset before 34 weeks' gestation in women with inheritable thrombophilia and prior delivery for pre-eclampsia/IUGR before 34 weeks [26].

In summary, although combined treatment with aspirin and LMWH appears to have improved perinatal outcome in some women with a poor obstetric history and inherited thrombophilias, there is a lack of clear evidence from large trials. Large adequately powered randomized controlled trials are needed before definitive recommendations can be made about the treatment of thrombophilias in pregnancy. The Thrombophilia in Pregnancy Prophylaxis Study (TIPPS) is underway (ClinicalTrials.gov identifier: NCT00967382). This trial seeks to determine the safety and effectiveness of LMWH in preventing placenta-mediated pregnancy complications and venous thromboembolism in women with thrombophilia. Until the uncertainties surrounding the management of thrombophilias are resolved, decisions about antithrombotic therapy in women with thrombophilia and pregnancy complications should be based on an individual risk/benefit assessment. Assessment of the maternal thrombotic risk during pregnancy should also be incorporated into the decision-making process regarding prophylaxis.

6.11 Unresolved Issues

6.11.1 Fetal Genotype

While there have been some reports that fetal thrombophilia status is important for the outcome of pregnancy [28], there are a several reasons to

suggest that this may not be the case. First, most thrombophilic polymorphisms are mild risk factors for gestational vascular complications and gestational thromboembolism. Second, thrombotic changes are noted mainly on the maternal side of the uteroplacental unit. Third, LMWH that does not cross the placenta is beneficial. Thus, unless there is a severe thrombophilic defect (i.e. homozygous protein C deficiency), fetal thrombophilic state is probably not a major contributor to gestational vascular complications or thromboembolism. However, further data from studies addressing the triad of mother, father and fetus are needed to clarify this issue.

6.11.2 Women with Unexplained Pregnancy Loss

When evaluation for the current known thrombophilias is negative, it is theoretically possible that an as yet undiscovered thrombophilia may be implicated in placental thrombotic changes found in women with gestational vascular complications. Following preliminary experience with antithrombotic therapy in these women [99], prospective randomized multicenter trials are currently underway.

6.12 Future Perspectives

A number of issues in this field need to be addressed. First, 30–50 % of vascular gestational pathologies cannot be accounted for by the currently available tests for thrombophilia. Whether other genetic or acquired thrombophilias will be found to play a role remains to be determined. Polymorphisms at the thrombomodulin and endothelial protein C receptor genes [34, 80] may be associated with recurrent fetal loss. It has also been suggested that circulating microparticles may play a role in unexplained fetal loss [62]. While the mechanism(s) involved in the development of vascular gestational pathologies has(ve) not been established, it is intriguing to speculate whether antithrombotic strategies will be of value in this setting [41].

Management of the obstetric patient with thrombophilia, or an obstetric history that could be associated with thrombophilia, is controversial due to the fact that there are no evidence-based guidelines directing all aspects of management. Finally, the role of antithrombotic treatment should continue to be explored in prospective clinical trials, in the hope of improving gestational outcomes in this large population of women.

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